Superselective Intra-Arterial Chemotherapy With Mitomycin C in Hepatic Metastases From Colorectal Cancer

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Background: Mitomycin C has been found clinically useful in the treatment of colorectal cancer when administered via the hepatic artery. In a prospective therapeutic trial, we studied the effect of superselective intra-arterial chemotherapy with mitomycin C in patients with hepatic metastases from colorectal cancer.

Methods: Forty-six patients with hepatic metastases from colorectral cancer received intra-arterial chemotherapy with mitomycin C (SIAC) between 1981 and 1991. The results of a 5-year follow-up were compared with 46 control patients standardized by sex, age, and tumor distribution.

Results: The overall response rate to intra-arterial chemotherapy was 20%. The median survival time for responders was 26 months and that for nonresponders 12 months ($P < 0.003$). The median survival period after intra-arterial chemotherapy was 15 months, compared with 9 months in controls ($P < 0.004$). The cumulative 5-year survival rate was 6% for patients treated by SIAC and 5% for controls. Cessation of chemotherapy was necessary in 39 of the 46 patients: in 28 because of tumor progression, in 9 because of toxicity, in 1 because of catheterization difficulties, and in 1 because of patient refusal.

Conclusions: Superselective intra-arterial mitomycin C therapy had a poor effect on hepatic metastases from colorectal cancer because of the low response and long-term survival rates.

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KEY WORDS: chemotherapy; hepatic artery infusion therapy; colorectal cancer; hepatic metastases

INTRODUCTION

The liver is the most common site of distant metastases from colorectal cancer [1], and hepatic resection still represents the best chance to improve long-term survival with acceptable mortality and morbidity [2]. However, because ~5% of colorectal cancer patients fall into this category, resection of hepatic metastases can improve the overall survival of patients with colorectal cancer by only 1–2% [3]. When surgery is no longer warranted, hepatic artery chemotherapy has been used to treat those patients with metastases confined to the liver.

In theory, regional chemotherapy delivers a high concentration of the drug to the liver, mostly avoiding high serum concentrations, which decreases systemic toxicity [4]. Mitomycin C has been used as a broad-spectrum anti-cancer drug for two decades, and it is of clinical utility in the treatment of colorectal cancer when administered by the hepatic artery route. We started a prospective therapeutic trial on patients with hepatic cancer, carcinoma of the gallbladder, and hepatic metastases of

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colorectal cancer in 1981 to examine the effect of superselective intra-arterial chemotherapy (SIAC) with mitomycin. We earlier reported the results concerning hepatic cancer [5] and cancer of the gallbladder [6]. This report covers the results of 46 patients with hepatic metastases from colorectal cancer, comparing them with control patients treated without anticancer drugs during the same period and standardized by sex, age, and dissemination of the disease.

MATERIALS AND METHODS

During a 12-year period from January 1981 to December 1991, 46 patients at the Oulu University Hospital, with histologically proven hepatic metastases from colorectal cancer, were subjected to a prospective treatment trial with superselective intra-arterial chemotherapy using mitomycin C (SIAC). All the 46 patients volunteered, accepting the risk of the treatment, which treatment was carried out in accordance with the propositions of the Declaration of Helsinki. During the same period, 115 other colorectal cancer patients with hepatic metastases were treated at our hospital. From among these 115 patients, 46 control patients with corresponding age, sex, and tumor distribution were chosen. Patient characteristics are presented in Table I.

TABLE I. Clinical Characteristics of SIAC and Control Groups of Patients With Hepatic Metastases From Colorectal Cancer

Characteristics	SIAC[a] group (N = 48)	Control group (N = 48)
Sex		
Men	27	27
Women	19	19
Age		
Mean (standard deviation)	59 (14)	61 (11)
Range	37–78	38–82
Primary tumor		
Dukes A	3	2
Dukes B	10	9
Dukes C	14	16
Dukes D	20	18
Liver metastases		
Primary	18	16
Secondary	28	30
Distribution		
Unilobar	24	26
Bilobar	22	20
Tumors		
Solitary	16	16
Multiple	30	30
Diameter		
< 5 cm	30	29
5–10 cm	16	17
Risk factors		
No risk factors	27	25
Adverse risk factors	19	21
Hepatic replacement rate		
Stage 1	20	15
Stage 2	13	9
Stage 3	7	11
Stage 4	6	11

[a]Superselective intra-arterial chemotherapy using mitomycin C.

All the 92 patients underwent resection of the primary tumor, 18 in the SIAC group and 16 in the control group having hepatic metastases at the time of primary surgery and 28 and 30 patients developing them later, respectively. The diagnosis was confirmed at laparotomy (18/16), or with either ultrasound (18/16) or computed tomography (6/3) and fine-needle biopsy. The diagnostic delay was defined as the period between the primary surgery and the confirmed diagnosis of metastases. Thirty-seven patients received SIAC as the primary therapy after the detection of hepatic metastases and nine as additional therapy because of irradicality of surgery.

Selective coeliac axis and superior mesenteric angiography were always performed before SIAC. Mitomycin C, 20 mg diluted in 200 ml of normal saline, was then infused into the common hepatic artery or in some cases even more selectively over a 30-minute period. If angiography revealed an accessory right hepatic artery originating from the superior mesenteric artery, or a left hepatic artery originating from the left gastric artery, the infusion was divided in two, and half of the solution was injected into each artery feeding the tumor area. This selective catheterization and initial infusion of 15–20 mg of mitomycin C was repeated at 6-week intervals with 10 mg of mitomycin C up to a total dose of 75–100 mg or until toxic reactions or tumor progression precluded further chemotherapy.

The patients were staged by ultrasound and computed tomography and direct exploration at laparotomy. The staging system was a refinement of the percentage hepatic replacement (PHR) system [7,8]: Stage I PHR <25%, Stage II PHR 25–75%, Stage III PHR >75%, and Stage IV extrahepatic disease. The primary tumors were classified according to the Dukes classification using Turnbull's modification [9].

The response to chemotherapy was studied by ultrasound and CT before each infusion of mitomycin. A response was defined according to the World Health Organization (WHO) criteria as complete if there was total disappearance of all lesions and as partial if there was a decrease of the total bulk of all lesions by at least 50%.

The effect of the presence or absence of various risk factors (Stage III or IV disease, clinical jaundice, ascites, serum bilirubin level >50 micromol/L, alkaline phosphatase level >240 units/L) on median survival was evaluated by the Mann-Whitney U-test. Survival was measured from the time of a confirmed diagnosis of recurrent disease, all patients being followed up until August 1996 or until death. The survival curves were calculated using

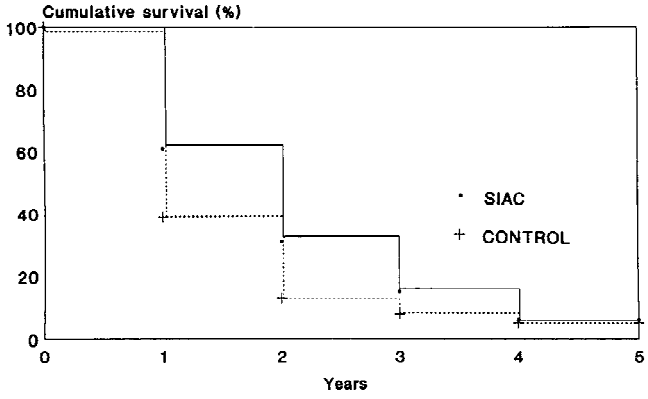

Fig. 1. Cumulative 5-year survival rate of patients treated by superselective intra-arterial chemotherapy with mitomycin C (SIAC) did not differ significantly from that of the control patients (log rank test).

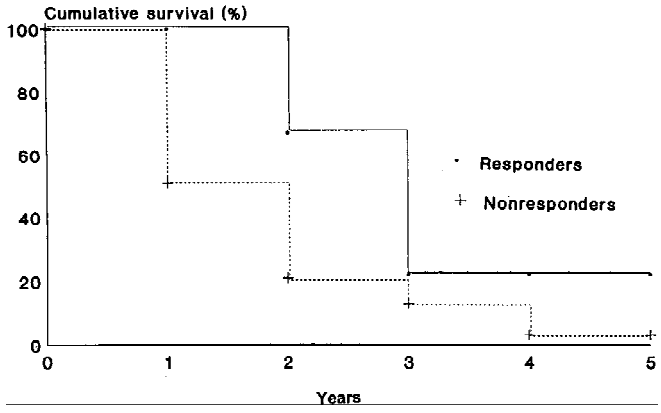

Fig. 2. The patients who responded to superselective intra-arterial chemotherapy with mitomycin C (SIAC) had a significantly better cumulative survival than those who did not respond ($P < 0.003$, log rank test).

the life-table method [10], and the log-rank test was used to determine differences between survival curves. $P < 0.05$ was considered significant.

RESULTS

The diagnostic delay did not differ between the groups. The mean delay was 11 ± 13 months (range 0–60 months) in the SIAC group and 15 ± 15 months (range 0–59 months) in the control group.

The removal of hepatic metastases was achieved in nine patients of the SIAC group and in seven patients of the control group at surgery, one of the patients in both groups being a long-term survivor. The overall 5-year survivals did not differ between the groups, being 6% in the SIAC and 5% in the control group (Fig. 1), but the difference between median survivals, 15 months and 9 months, was significant ($P < 0.004$). When the resected patients were excluded, the cumulative 5-year survival was 3% in both groups and the median survivals were 13 and 7 months, respectively. The median survival of the resected patients was 25 months after mitomycin C infusion and 12 months in the control group.

Of the 46 patients in the SIAC group, two showed a complete response and seven a partial response. This gave an overall response rate of 20% (9/46). The median survival time for the responders was 26 months and that for the nonresponders 12 months ($P < 0.003$), and the cumulative 5-year survivals were 22% and 3% (Fig. 2).

The patients with no risk factors who received intra-arterial chemotherapy survived for a median of 18 months and those with one or more risk factors for 10 months. In the control group, the median survival time was 12 months with no risk factors and 5 months with adverse risk factors (Table II). All patients with ascites died within 5 months and all jaundiced patients within 10 months.

The median survival time for the patients in the SIAC croup was longer at all stages of PHR than in the control group and significantly longer at stages III and IV (Table III), but cumulative survival did not differ significantly at any stage. All patients at stages III and IV died within 24 months.

TABLE II. Effect of Risk Factors on Survival in Patients With Hepatic Metastasis From Colorectal Cancer

	SIAC[a] group		Control group	
Survival	No risk factors	Adverse risk factors	No risk factors	Adverse risk factors
Median (months)	18	10	12	5*
At 1 year (%)	67	53	52	24
At 3 years (%)	18	11	12	4
At 5 years (%)	6	6	7	0

[a]Superselective intra-arterial chemotherapy using mitomycin C.
*$P < 0.016$ when compared with the patients with adverse risk factors in the SIAC group.

Chemotherapy had to be discontinued in 39 of the 46 patients (85%) and the total dose was >75 mg in 15% (7/46), 50–75 mg in 31% (14/46), and <50 mg in 54% (25/46) of the patients. The most frequent causes of cessation were tumor progression, 61% (28/46) and gastrointestinal toxicity, 13% (6/46). The latter included diarrhea and vomiting in four patients and gastric ulcers in two patients. Myelotoxicity developed in three patients and included two patients with thrombocytopenia and one patient with leukopenia. One patient refused additional treatment, and in one case catheterization difficulties were the cause of cessation. Of the seven patients who received full therapy, three are still alive, and the median survival in this subgroup was 28 months.

DISCUSSION

The treatment of hepatic metastases of colorectal cancer continues to carry a dismal prognosis in spite of the progress made in various forms of modern chemo-

TABLE III. Survival of Patients With Metastases of Colorectal Cancer

	SIAC[a] group				Control group			
	Stages				Stages			
Survival	I	II	III	IV	I	II	III	IV
Median (months)	19	14	10	8	15	8	5*	4*
Cumulative survival (%)								
At 1 year	80	54	28	50	53	33	9	9
At 2 years	40	31	0	0	20	11	0	0
At 5 years	7	15	0	0	7	11	0	0

[a]Superselective intra-arterial chemotherapy using mitomycin C.
*$P < 0.05$ when compared with corresponding patients treated with SIAC.

therapy. We started a new prospective trial in 1981, administering mitomycin C through superselective intra-arterial infusion. Mitomycin C was chosen because it has been claimed that colorectal cancer is responsive to it [11] and it can be used at 6-week intervals. It was later reported to have additional advantages, such as dose-related cytotoxic action [12], elimination of mitomycin in the liver [13], preferential activation of cytotoxic metabolites at hypoxic tumor cells [14], and entry into the enterohepatic circulation [15]. The effect of this therapy on hepatic metastases of colorectal cancer, however, can be reliably estimated only after long-term follow-up.

Long-term results show that hepatic resection still provides the best possibilities for permanent cure from hepatic metastases of colorectal cancer [2,16]. Promising results of chemotherapy have been reported in small series with implantable pumps [17,18], with targeted microsphere-based regional 5-FU chemotherapy [19], and with mitomycin C-loaded microcapsules infused intra-arterially into the liver [20].

The median survival after SIAC was 15 months, but all the long-term survivors, except one patient with small metastases in the right lobe, had undergone hepatic resection. Thus we must admit that SIAC was not able to prevent overall progression of the tumor or lengthen the long-term survival of patients with unresected liver metastases from colorectal cancer.

The response rate after SIAC remained disappointingly low, 20%, and only two of the responders had complete response, one of them being the long-term survivor without resective surgery of hepatic secondaries. Using combination therapy including mitomycin C, better total response rates of 26–39% have been recently reported [21,22], but despite the good preclinical evidence of the efficacy of mitomycin [23], we think that the resistance of advanced colorectal cancer cannot be beaten using SIAC.

The adverse risk factors reflect the severity of the disease, but their existence does not preclude further treatment. The patients with adverse risk factors showed longer median survival with SIAC in the present series, which is naturally at least partly due to patient selection.

The extent of tumor involvement in the liver has been regarded as an important prognostic variable with respect to chemotherapy [24,25]. Stage I and II tumors were associated with a more favorable outcome in the present study, but without any statistical difference between the SIAC and control groups. At stages III and IV, the survival figure was poor. At these stages, the median survivals were longer after intra-arterial mitomycin chemotherapy, but this is probably a bias due also to patient selection.

Morbidity related to SIAC was high, 22%, and 85% of the patients required cessation of therapy prior to the full dose. We agree with Krakoff [26] that it is a major responsibility for the physician to recognize the time when active antitumor therapy ceases to have a rational basis. The better survival of our responders was ruined by a poor response rate, which made the overall treatment results poor.

CONCLUSION

Our results indicate that although this form of chemotherapy prolongs the median survival, it does not provide a better long-term survival for patients with hepatic metastases from colorectal cancer.

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